The Epidemiology of Schizophrenia reflects Pathology of Neurodevelopment and Striatal Dopamine

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Mapping of Epidemiology onto Pathogenesis

- It is commonplace in medicine for the epidemiology of a disease to be readily interpretable in terms of the pathogenesis of the disorder.

- For example, the risk factors for Coronary Heart Disease all ultimately cause atherosclerotic damage to the endothelium of the coronary arteries – the final common pathway.

- The different risk factors increase the likelihood of plaque formation by different mechanisms.

- For example, family history is associated with increased LDL cholesterol, smoking increases platelet adhesion, hypertension damages the endothelium.
Epidemiology and Pathogenesis are not integrated in Schizophrenia

- Epidemiological research has made major advances in the last ten years.

- However, this research has proceeded separately from research into the two major pathogenic theories, the neurodevelopmental and dopamine hypotheses.

- Have we reached a point where we can begin to integrate epidemiological findings with pathogenetic theory?
Epidemiological Fact 1

- Schizophrenia shows a modest tendency to run in families.
The risk to the identical co-twin of a Schizophrenic individual is about 50%.

Since 2002 a number of susceptibility genes have been reported.

**Genes involved in Neurodevelopment**
- Neuregulin
- Dysbindin
- DISC 1
- Neurexin

**Genes involved in Neurotransmission**
- DRD2
- DAT
- COMT
- AKT1
Nature held a Press Conference in summer 2009 when 3 GWAS studies reported more risk genes for schizophrenia.
There may be hundreds of risk genes for schizophrenia.

Do I have any?
Now we know there are >100 genes, this is more compatible with the idea that there is a continuum of liability to psychosis.
SURPRISE! - Copy Number Variants

Copy Number Variations account for at least 10% of Autism

Might they account for some cases of schizophrenia?
Copy Number Variants (CNVs) are found in Excess in Schizophrenia

Large recurrent microdeletions associated with Schizophrenia

Effect of CNVs and Mens’ Cars

Ferraris have a very big effect on individual girls but they are rare and therefore may explain only 5% of overall male attractiveness. Similarly, CNVs have a big effect on risk of Sz but explain only 5% of cases.

Corollas have a very small effect on individual girls but because they are so common overall, they may explain 30% of overall effect. Similarly common variants like neuregulin have a small effect but this adds up.
- Copy Number Variations may account for a small proportion of schizophrenia (5%+)

- The CNVs implicated overlap with autism and mental handicap.

- They may account for some of the developmental impairment in schizophrenia

- Not so far reported in excess in Bipolar Disorder (Grozeva et al, 2010)
Epidemiological Fact 2

- Schizophrenia but not bipolar disorder is associated with childhood cognitive and neuromotor impairments
Dunedin Study: Motor and language development in pre-symptomatic children

Pre-schizophreniform

Pre-manic

Mary Cannon et al 2002
Swedish Cohort Study

At age 15, graded in 16 subjects

280 Bipolar
493 Schizophrenia

MacCabe et al 2009
Risk of schizophrenia in 716,000 Swedish people according to scholastic ratings

MacCabe et al 2009
Risk of bipolar disorder in 716,000 Swedish people according to scholastic ratings

MacCabe et al 2009
Epidemiological Fact 3

- Exposure to obstetric events especially hypoxia increases risk of schizophrenia but not bipolar disorder
Dunedin Study: those who met criteria for schizophreniform disorder at 26 years, compared to controls, showed:

- Higher overall obstetric complications ($t=5.5; p<0.001$)
- Higher neonatal insults ($t=5.95; p<0.001$)
- Smaller for gestational age (OR=2.8; $p<0.001$)
- More Hypoxia (OR=6.8; $p<0.001$)

Meta-analysis shown no excess of obstetric complications in bipolar disorder (Scott et al)
Developmental cascade towards schizophrenia

Pre & perinatal events

Subtle motor, cognitive and social deficits

Social anxiety, depression

Quasi psychotic ideas

CNVs

Developmental Genes: eg NRG1; DISC1,
Developmental Models of Schizophrenia all implicate Dopamine

- Early lesion of hippocampus (hypoxic)
- MAM damage to hippocampus (prenatal)
- Vitamin D Deficiency Model
Dysregulation of the Dopamine System – the Final Common Pathway to Schizophrenia?*

*This is not to deny the role of GABA, glutamate, endocannabinoids
When does the Striatal DA abnormality arise?

18F-Dopa Uptake: presynaptic dopamine synthesis
Dopamine is the “Wind of Psychotic Fire”

- When individuals are acutely psychotic, they show an excessive striatal release of dopamine\(^1\)
- Dopamine is involved in reward learning and normally mediates the attachment of salience to ideas and objects\(^2\)
- Excessive dopamine release leads to aberrant assignment of salience to unimportant stimuli\(^3\)
- Delusions arise from attempts to explain this abnormal salience\(^4\)

\(^1\) Laruelle et al 1996; \(^2\) Berridge and Robinson 1998; \(^3\) Kapur 2003; \(^4\) Maher 1983
Developmental cascade towards schizophrenia

Pre & perinatal events

1. Subtle motor, cognitive and social deficits
2. Social anxiety, depression
3. Quasi psychotic ideas
4. Dopamine Dysregulation of Salience

CNVs
Developmental Genes: eg NRG1; DISC1, BDNF
Stimulant drugs can produce a schizophrenia-like picture.
Psychopathology of individuals with methamphetamine psychosis

Chen et al Psychological Medicine 2003
Developmental cascade towards schizophrenia

Pre & perinatal events

Subtle motor, cognitive and social deficits

Social anxiety, depression

Quasi psychotic ideas

Drug abuse

Dopamine Dysregulation of Salience

CNVs

Developmental Genes: e.g. NRG1; DISC1, BDNF
Epidemiological Fact 5

- Schizophrenia has its maximum onset in early adult life and thereafter incidence declines.
Rates of schizophrenia per 100,000 population in Camberwell

Age at onset (years)

- Males
During reward anticipation younger subjects recruit the ventral striatum and anterior cingulate to a greater extent than older subjects.
Epidemiological Fact 6

- Certain types of social adversity increase risk of schizophrenia
ÆSOP Study – Social Factors that increase the risk of schizophrenia

Hypothesis: social defeat is a risk factor for schizophrenia?

JEAN-PAUL SELTEN and ELIZABETH CANTOR-GRAAE

Mesolimbic Dopamine System can be altered by Social Manipulation

- Isolation rearing increases DA release in response to amphetamine in adult rats

- PET Scan study of changing housing of primates shows differences in dopamine receptor occupancy between the subordinate and dominant animal

- Placing a mouse in with a “Bully” alters expression of BDNF and therefore the Dopamine system
Dopamine Release in Response to a Psychological Stress in Humans and Its Relationship to Early Life Maternal Care: A Positron Emission Tomography Study Using $^{[11]}$C]Raclopride

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Cortisol levels in First Episode Psychosis

*55% increase in cortisol AUC

$p=0.001$

Awakening Noon 8:00 PM

Cortisol (nmol/l)

Patients < 2 weeks of treatment Controls

* Patients < 2 weeks of treatment
* Controls

* 55% increase in cortisol AUC

$p=0.001$
Increased cortisol is associated with hippocampal volume decrement

Mondelli et al, 2010

This is reminiscent of Tony Grace’s model in which the developmentally MAM damaged hippocampus suffers a second hit with resultant dysregulation of dopamine.
Developmental cascade towards dopamine dysregulation and schizophrenia

- Pre & perinatal events
- Early and late social adversity
- Drug abuse

Subtle motor, cognitive and social deficits
- Social anxiety, depression
- Quasi psychotic ideas
- Dopamine Dysregulation of Salience

CNVs
- Developmental Genes: eg NRG1; DISC1, BDNF

0 5 10 15 20
Conclusion

- Most of the epidemiological characteristics of schizophrenia can be understood in terms of abnormalities of neurodevelopment and of striatal dopamine.

- The challenge is now to accurately delineate the mechanistic pathways which link risk factors with development and dopamine and to devise ways of interfering with them.